David M Forrest, MD, MHSc, FRCPC
Infectious Diseases,
Nanaimo Regional General Hospital
1200 Dufferin Crescent,
Nanaimo, BC
V9S 2B7

February 1, 2012

Dr. JP Stewart,
Senior Executive Director,
Therapeutic Product Directorate,
Health Canada

Dear Sir,

I am writing to you today concerning the decision by Health Canada not to release clofazimine for compassionate use in the treatment of multi-drug resistant *Mycobacterium avium* complex (MAC) infection, where alternate therapies have failed or toxicities have precluded their use.

For over a year now, the Tuberculosis Control arm of the BCCDC has sought access to clofazimine on behalf of two patients in Central Vancouver Island who have evidence of refractory MAC pulmonary infection. In both cases, the patients have failed standard therapy and have not responded to use of second and third line agents, despite pharmacokinetic monitoring and consequent dosage adjustments to achieve therapeutic drug levels. They have developed significant toxicity (blindness due to optic neuritis due to ethambutol in one and vestibulotoxicity due to streptomycin in the other), which has further limited therapeutic options to add to an already failing regimen.

While I understand Health Canada's concerns about use of clofazimine for MAC therapy in non-compassionate circumstances, I am frankly appalled that Canadian citizens would be denied a potentially life-saving rescue therapy, which has been used widely throughout the world; which has known and relatively limited toxicity; for which there is clear evidence of *in vitro* efficacy; which has a long and successful track record in treatment of other mycobacterial diseases (leprosy), and for which there is no evidence of harm in such a patient group as mine (a previous study suggesting inefficacy only in the treatment of disseminated MAC infection in a cohort with advanced HIV disease, in which the treatment groups were unbalanced [the clofazimine treatment group with significantly higher levels of bacteremia, which in *post hoc* analysis correlated in a statistically significant fashion with outcome independent of treatment assignment – i.e., the higher level of bacteremia in the clofazimine group potentially explaining entirely the worse outcome in that treatment arm], and where utilized as first-line therapy). Further, the drug is cheap (available through Internet pharmacies for $40 for a 3 month supply). And there is sufficient evidence of its effectiveness to warrant consideration of its use as a *first-line* agent for this condition (a clinical trial of which Dr. Field is planning), not just salvage therapy.

Over the past six months, BCCDC TB Control has corresponded in writing and by telephone on multiple occasions about this matter, with continued denial of our request. I demand you write to me

directly to explain why Health Canada refuses to provide this potentially life-saving medication on a compassionate basis to Canadian citizens who have refractory MAC infection and/or intolerance of or toxicity to alternate agents. My patients have asked me to share your response with them.

I expect your immediate reply.

Sincerely,

David M Forrest, MD. MHSc. FRCPC

Infectious Diseases, NRGH

Cc Dr. V Cook, BCCDC, TB Control

Dr. S Field, University of Calgary

Honorable Dr. J Lunney, MP, Nanaimo-Alberni

Honorable L Aglukkaq, Federal Minister of Health

Right Honorable S Harper, Prime Minster. Canada

Mr. DR (patient)

Mrs. MSL (patient)

Health Canada | Santé Canada
Health Products and Food Branch | Direction générale des produits de santé et des aliments

Therapeutic Products Directorate
Holland Cross, Tower "B"
6th Floor, 1600 Scott Street
Address Locator # 3106B
OTTAWA, Ontario
K1A 0K9

FEB 14 2013

13-102352-947

Dr. David M. Forrest
Infectious Diseases
Nanaimo Regional General Hospital
1200 Dufferin Crescent
NANAIMO, British Columbia
V9S 2B7

Dear Dr. Forrest:

RE: Access to Clofazimine for *Mycobacterium avium complex* (MAC) Infection Patients

Thank you for your correspondence of February 1, 2013 regarding access to clofazimine for patients with multi-drug resistant *Mycobacterium avium complex* (MAC) infection.

As you are aware, the Special Access Programme (SAP) is meant to be used, on a case-by-case, to access un-marketed drugs for treating patients with serious or life-threatening conditions where other therapies have failed or are unsuitable or unavailable, and the decision to authorize or deny a request is based on the information provided by the practitioner. A request may be denied if the information in the request does not support the use of the drug for the patient for the indication listed.

At the present time, while the use of clofazimine in the treatment of leprosy is supported in the literature and recommended by the World Health Organization (WHO), its role in the treatment of MAC is not established. As you know, our overarching concern is that without robust data to support the safety and efficacy of clofazimine for MAC disease or any effort to gather such data, its actual clinical utility will remain unknown. Based on the information we have received from practitioners and review of the literature, at present, the best available evidence is limited to case-control studies and it is significant to us that none of these has prompted expert organizations such as the American Thoracic Society (ATS) or the Infectious Diseases Society of America (IDSA) to recommend any use of clofazimine in MAC. In fact the ATS/IDSA guideline on the Diagnosis,Treatment, and Prevention of Nontuberculous Mycobacterial Diseases (*Am J Respir Crit Care Med Vol 175. pp 367–416, 2007*) notes that the role of clofazimine for MAC is currently a controversy and an unresolved question in the field.

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As you know, Health Canada's Therapeutic Products Directorate held a teleconference on January 9, 2013, to provide practitioners an opportunity to discuss access to clofazimine for the indication of MAC via the SAP and clinical trials, and it is my understanding that you participated on that teleconference. As discussed on the call, the information received so far, does not support routine access to clofazimine for MAC via the SAP however, the Programme is open to receiving new literature or other supporting data. As such, you may wish to re-submit a request on behalf of your patients with supporting evidence, for SAP's consideration. If you have additional questions or require additional clarification feel free to contact the SAP directly at 613-941-2108.

As indicated during the teleconference, clinical trials is the mechanism recommended to provide access to non-marketed drugs as it ensures that the best interests of the patients are protected, while advancing the scientific knowledge on the safety and efficacy of a drug. You may wish to consider access by participating in the collaborative clinical trial being planned by Dr. Field, or you could also develop a separate protocol to address the needs of patients at your Centre. Should you wish to explore these options, I can direct you to the appropriate representatives within the Office of Clinical Trials.

Should you wish to discuss this letter further, please feel free to contact me directly.

Sincerely,

Dr. John Patrick Stewart
Interim/Senior Executive Director

HEALTH CANADA'S RESPONSE TO CBC
JUNE 6, 2013

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Q1: Why can some patients get special approval from HC while others can't?
Q2: Why is it apparently more difficult for doctors to get these special approvals now, compared to a year ago?

The health and safety of Canadians and patients is always the department's first priority. When Health Canada reviews an application of a drug under SAP, we assess the application based on the seriousness of the condition, the availability of other therapies, and information about the use, safety and efficacy of the drug.

Clofazimine does not have market authorization in Canada and thus has not gone through the thorough scientific safety review that all approved drugs must go through. Health Canada cannot compel a company to submit an application for market authorization. However, Clofazimine has been accessed on occasion by the Special Access Programme (SAP) for a number of years for both leprosy and mycobacterium avium complex (MAC) infection. It also does not have market authorization to treat MAC infection in the United States.

Clofazimine has an established use in the treatment of leprosy and continues to be recommended by international organizations. As such, SAP will generally authorize requests for access to clofazimine for physicians treating patients with leprosy, if the requests are complete and where other therapies have been tried or are considered unsuitable.

Periodically, the programme's medical and scientific staff evaluate whether ongoing access to the drug is appropriate. As part of this evaluation, a detailed review is conducted of the available medical literature and treatment guidelines for drugs that continue to be requested through the SAP, to ensure that any ongoing access to the drug is scientifically supported.

When Health Canada reviewed the effectiveness of clofazimine in the treatment of MAC, the department found that current literature does not support this use. Specifically, Health Canada noted that the most recent treatment guidelines for MAC infection state that a number of drugs, including clofazimine, were shown to have limited or no evidence of clinical efficacy. (An Official American Thoracic Society (ATS) for the Infectious Disease Society of America (IDSA) Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases, Am J Respir Crit Care Med Vol 175. pp 367–416, 2007).

The 2007 guideline from the ATS/ISDA on the Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases does not recommend the use of clofazimine for MAC and notes that the use of the drug in this condition is currently a controversial and an unresolved question in the field.

The World Health Organization (WHO) also reports that it has not found evidence of effectiveness in the treatment of MAC.

Q3: What is HC going to do now to help these patients get this drug?

Given the lack of evidence of the efficacy of the use of clofazimine to treat MAC infections, the department has decided to limited access to clofazimine for MAC infection and has advised physicians who were using the drug to collaborate on developing a clinical trial that could formally gather evidence with respect to the use, safety and efficacy of this treatment.

To assist physicians who would like to use clofazimine to treat MAC infections, Health Canada convened a recent teleconference to provide advice and direction on how these physicians and their respective

institutions can sponsor a clinical trial. The department suggests that the trial could be up and running in a matter of months. Providing access to the drug under a clinical trial helps ensures patient protection (e.g. quality of the manufactured drug, patient informed consent, Research Ethics Board approval), and ensures that the information will be obtained from the trial, which can be further used to inform health care practitioners on the role of Clofazimine for the treatment of MAC infection.

Health Canada will continue to provide advice and direction about clinical trials to doctors who are interested in the use of clofazimine to treat MAC infections. Indeed, it has corresponded with lead physicians in the last few weeks.

It's important to note that SAP is not intended to be a mechanism to promote or encourage the early use of drugs or to circumvent the clinical trials review and approval process or the new drug approval process, but rather to provide emergency access to drugs on a patient by patient basis.

Q4: Given it has few if any side effects (we are told) why not just approve it whenever doctors request it?

Health Canada has strict requirements that drug manufacturers must meet before they can get sell a drug on the Canadian market. Drugs are only approved after Health Canada has thoroughly reviewed the scientific evidence provided and is confident that the drug is safe and effective when used as directed. This regulatory system is essential to protecting the safety of Canadians and their families. The SAP is not meant as a means to circumvent the regulatory process.

All drugs have side effects and clofazimine is no exception. Clofazimine's serious side effects, including diarrhea, bloody stool, stomach or abdominal pain, and mental depression.

As with the approval of all medications, Health Canada must consider both the risks and the benefits of a drug. To date, because there has been no evidence of benefit in the use of clofazimine for MAC infection from well designed clinical trials, there is potential that clofazimine could harm patients unnecessarily.

In deciding whether access to an unapproved therapy for a particular patient is appropriate, Health Canada reaches out to its internal and, where necessary, external expertise, to ensure the department is fully informed in determining the decision around providing access. As a federal regulator of therapeutic products, Health Canada has access to important information and resources that is factored into rendering a final decision on a particular request.

Health Canada acknowledges that for approximately the last decade experts have speculated about a potential role for the drug in MAC infection but to date there has been no concerted effort to test these theories through proper testing and clinical trials. Consequently, there is no evidence to support any routine use at this time.

Should new evidence come to light, Health Canada will take these findings under consideration.

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Blossom Leung
Media Relations Officer | Agente des relations avec les médias
Communications and Public Affairs Branch | Direction générale des affaires publiques et des communications
Health Canada | Santé Canada
(t) 613.946.0668
(e) blossom.leung@hc-sc.gc.ca
Government of Canada | Gouvernement du Canada

Drug Company's Statement

Date: Thu, Jun 6, 2013 at 9:51 AM

Subject: Media Inquiry for Novartis Regarding Lamprene

Dear Kathy,

Thank you for your inquiry regarding clofazimine (LampreneTM). Patients are the center of all we do at Novartis. The issue of access to medicines is complex, involving factors including development and health policies, health-system infrastructure and best practices, pricing, rational medicine use and adequate funding. While the fundamental aspects of healthcare provision are the responsibility of governments and intergovernmental agencies, Novartis, whenever possible, plays a supporting role to improve patient access to our medicines.

At Novartis, our drug discovery priorities are determined by patient need and sound science. For more than a decade, Novartis has been a leader in the discovery and development of innovative therapies to treat rare diseases, from rare forms of cancer to debilitating genetic diseases.

Globally, Novartis has 12 such drugs on the market, a robust clinical pipeline and currently more than 40 research projects to address the unmet medical need of rare diseases. Novartis is committed to finding treatments for rare diseases that impact both the life expectancy and quality of life for patients living with a rare disease as well as to raising awareness of rare diseases.

As you may know, clofazimine is approved for use in leprosy. The World Health Organization (WHO) cites that the “off-label” use of clofazimine is actively discouraged because it is a first line drug for the treatment of leprosy, and its indiscriminate use must be guarded against to prevent resistance.” The WHO recognizes that “some countries have started using the drug in the treatment of multi-drug resistant tuberculosis (MDR TB) and in mycobacterium avium complex (MAC) infections in acquired immune deficiency syndome (AIDS), but WHO has found no evidence of its effectiveness for these forms of treatment. However, if the intended use is for MDR-TB the request is referred to TB colleagues at WHO for their appraisal and possible approval, on a named patient basis. It should be noted that approval is only made on an exceptional basis.” Reference: (http://www.who.int/lep/mdt/clofazimine/en/index.html

We would encourage you to connect with Health Canada directly to clarify some of the Health Canada related questions in your inquiry.

Best regards, Andrea

Andrea Gilpin, Ph.D, MBA

Director, Corporate Communications

Novartis Pharmaceuticals Canada Inc.